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**CONFIDENTIAL TREATMENT REQUESTED**

April 12, 2004

## Carboplatin

Dear Mr. Clark:

Pursuant to Section XII, subsection (2) of the Decision and Order dated April 14, 2003 and 16 C.F.R. § 1.2, Bristol-Myers Squibb Company ("BMS") submits the enclosed agreement for the FTC's review. BMS requests that the FTC issue an advisory opinion finding that the agreement does not raise issues under Section 5 of the Federal Trade Commission Act.

The agreement, between BMS and Teva Pharmaceuticals USA, Inc. ("Teva") will resolve an ANDA patent litigation concerning the drug Carboplatin and U.S. Patent No. 4,657,927 (the "'927 patent"). BMS and Research Corporation Technologies ("RCT") prevailed in the district court, where infringement and enforceability were conceded, and summary judgment of no invalidity was entered. The Federal Circuit, in a 2-1 decision, vacated that judgment and directed that the case be remanded to the district court for further proceedings. BMS and RCT filed a motion for rehearing en banc, and the Federal Circuit is not expected to rule on that motion. The '927 patent is due to expire on April 14, 2004. However, BMS has filed with the FDA for pediatric exclusivity, based on having conducted a pediatric clinical trial, as requested by the FDA. If granted by the FDA, the pediatric exclusivity would result in a further six months of exclusivity for BMS.

BMS and Teva have agreed, subject to regulatory review, to settle their dispute on the terms set forth in the enclosed agreement. In substance, the agreement provides that the litigation will be dismissed and, if regulatory approval is granted, Teva

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will distribute an unbranded, generic version of BMS's product as of June 24, 2004, well before the six-month pediatric exclusivity would expire.

We respectfully submit that this agreement is both pro-competitive and fully consistent with the spirit of Section XII of the Decision and Order. We therefore request a favorable determination from the FTC.

To aid the FTC's evaluation of this request, I am enclosing the following materials:

1. U.S. Patent No. 4,657,927;
2. Memorandum Opinion and Order, Bristol-Myers Squibb Company and Research Corporation Technologies, Inc. v. Pharmachemie B.V., C.A. No. 01-3751 (MLC) (D.N.J. July 29, 2002);
3. Final Judgment, Bristol-Myers Squibb Company and Research Corporation Technologies, Inc. v. Pharmachemie B.V., C.A. No. 01-3751 (MLC) (D.N.J. Oct. 22, 2002);
4. Decision, Bristol-Myers Squibb Company and Research Corporation Technologies, Inc. v. Pharmachemie B.V., Appeal No. 03-1077 (Fed. Cir. Mar. 17, 2004);
5. Carboplatin for Injection Distribution Agreement (April 8, 2004);  
and
6. Letter from Robert L. Baechtold to Clerk of U.S. Court of Appeals for the Federal Circuit (April 8, 2004).

As time is of the essence, we respectfully request expedited treatment of this request. The FTC's response is requested as soon as possible and before June 10, 2004. Due to the time-sensitive nature of this agreement, its implementation will not be possible without such expedited review.

Confidential treatment of this letter and the enclosed materials is respectfully requested.

If you have any questions, please do not hesitate to call me at the number above.

Thank you in advance for your consideration and assistance.

Respectfully,



Richard J. Stark

Donald Clark, Secretary  
Federal Trade Commission  
6<sup>th</sup> Street and Pennsylvania Avenue, N.W.  
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Encls.

BY FEDERAL EXPRESS

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**United States Patent** [19]

**Cleare et al.**

[11] **Patent Number:** **4,657,927**

[45] **Date of Patent:** **Apr. 14, 1987**

[54] **MALONATO PLATINUM COMPOUNDS**

[75] **Inventors:** Michael J. Cleare; James D. Hoeschele; Barnett Rosenberg; Loretta Van Camp, all of East Lansing, Mich.

[73] **Assignee:** Research Corporation, New York, N.Y.

[21] **Appl. No.:** 497,806

[22] **Filed:** May 25, 1983

**Related U.S. Application Data**

[62] **Division of Ser. No. 902,706, May 4, 1978, abandoned.**

[51] **Int. Cl.<sup>4</sup> .....** A61K 31/28

[52] **U.S. Cl. ....** 514/492

[58] **Field of Search .....** 424/287; 514/492

*Primary Examiner*—Jerome D. Goldberg  
*Attorney, Agent, or Firm*—Scully, Scott, Murphy & Presser

[57] **ABSTRACT**

Malonato platinum coordination compounds and a method of treating malignant tumors sensitive to a planar  $dsp^2$  platinum (II) coordination compound or an octahedral  $d^2sp^3$  platinum (IV) coordination compound comprising the parenteral administration to an affected animal of a solution of the compound.

**4 Claims, No Drawings**

## MALONATO PLATINUM COMPOUNDS

This is a Divisional, of Application Ser. No. 902,706, filed May 4, 1978, abandoned.

## BACKGROUND OF THE INVENTION

The present invention relates to novel malonato platinum coordination compounds and to their use in cancer chemotherapy.

## SUMMARY OF THE INVENTION

The invention provides platinum coordination compounds having the formula:



or



wherein:

x=1 or 2;

y=1 or 2;

z=0, 1 or 2, provided that when y=2, z=0 and when y=1, z is greater than 0;

R and R<sub>1</sub> are selected from the group consisting of H, lower alkyl, aryl, aralkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, OH, or are combined with the carbon atom to form a cycloalkyl or cycloalkenyl group, and substituted derivatives thereof;

when x=1, A is HR<sub>2</sub>N-CHR<sub>3</sub>-CHR<sub>4</sub>-NR<sub>5</sub>H and when x=2, A is H<sub>2</sub>NR<sub>6</sub> a heterocyclic amine or an amino acid, wherein R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are the same or different and are selected from the group consisting of H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, hydroxy and lower alkoxy provided that R<sub>2</sub> and R<sub>5</sub> may also be aryl or aralkyl, and each R<sub>5</sub> is the same or different and is selected from the group consisting of H, lower alkyl, aryl, aralkyl, hydroxy lower alkyl, hydroxyl and alkoxy amines, alkoxyalkylamines wherein all of said alkyl groups are lower alkyls and heterocyclic substituents including said N as a ring member;

when z=1, L is a bidentate anionic ligand, and when z=2, L is a monodentate anionic ligand.

The invention also relates to a composition and method for treating malignant tumors sensitive to a planar dsp<sup>2</sup> platinum(II) coordination compound or an octahedral d<sup>2</sup>sp<sup>3</sup> platinum(IV) coordination compound in animals comprising parenterally administering to an animal affected with such a malignant tumor a solution containing a platinum coordination compound as defined hereinabove in an amount sufficient to cause regression of the tumor.

## DETAILED DESCRIPTION OF THE INVENTION

Platinum coordination compounds and methods for their production are described by J. C. Bailar, Jr., *The Chemistry of the Coordination Compounds*, Reinhold Publishing Corp., N.Y., 1956, Chap. 2; J. Lewis et al, *Modern Coordination Chemistry: Principles and Methods*, Interscience Publishers, Inc., N.Y., 1960 and Kauffman *Inorganic Synthesis*, 7, McGraw-Hill Book Co., Inc., N.Y., 1963.

Platinum(II) forms dsp<sup>2</sup> coordination compounds which have a square planar arrangement in space. Plat-

num(IV) forms d<sup>2</sup>sp<sup>3</sup> coordination compounds which have an octahedral arrangement in space.

The coordination compounds of the invention include the cis and trans isomers of platinum(II) and platinum(IV) which contain the bidentate malonato ligand which may be substituted or unsubstituted. The malonato ligand may contain substituents selected from the group consisting of lower alkyl, (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, etc.); aryl, (e.g., phenyl; lower alkyl-, lower alkenyl-, halo-, nitro-, lower alkoxy-substituted phenyl and naphthyl); aralkyl, (e.g., phenylmethyl(benzyl), 2-(1-naphthyl)methyl); alkenyl, (e.g., 4-amino-1-butene, allyl); cycloalkyl, (e.g., cyclopropyl, cyclohexyl, etc.); cycloalkenyl, (e.g., 2-cyclopenten-1-yl, 2-cyclohexen-1-yl); alkoxy, (e.g., methoxy, ethoxy, etc.), and hydroxy. Also suitable are the 1,1-cycloalkylenedicarboxylic acids, (e.g., 1,1-cyclopropanedicarboxylic acid, 1,1-cyclobutanedicarboxylic acid, etc.) and the 1,1-cycloalkenyldicarboxylic acids, (e.g., 1,1-cyclopropenyldicarboxylic acid, 1,1-cyclobutenedicarboxylic acid, etc.)

The coordination compounds of the invention also contain two monodentate ammonia or primary or heterocyclic amine ligands, i.e., when x in the above formula is 2 or one bidentate amine liquid, i.e., when x is 1.

Suitable monodentate amine ligands include lower alkyl amines, (e.g., methyl-, ethyl-, n-propyl-, isopropyl-, n-butyl- amines, etc.), aryl amines, (e.g., aniline), aralkyl amines, (e.g., benzylamine), hydroxy lower alkyl amines, (e.g., ethanolamine, propanolamine, etc), hydroxylamine, lower alkoxy amines (e.g., methoxylamine, etc.), alkoxyalkylamines (e.g., methoxymethylamine, etc.), and heterocyclic amines (e.g., pyridine and aziridine). Also included are the amino acids, i.e., R<sub>7</sub>-CHNH<sub>2</sub>-COOH wherein R<sub>7</sub> is H, lower alkyl (e.g., methyl, isopropyl, etc.), hydroxy lower alkyl (e.g., hydroxymethyl, hydroxyethyl, etc.), aralkyl (e.g., benzyl, etc.).

It is to be understood that the coordination compounds of the invention may include two identical or different monodentate ligands.

Suitable bidentate amine ligands include the substituted and unsubstituted primary and secondary ethylenediamines. One or both of the carbon atoms of the ethylenediamine may contain substituents such as lower alkyl (e.g., methyl, ethyl), hydroxyl, alkoxy (e.g., methoxy, ethoxy, etc). Secondary ethylenediamines wherein one or more of the amine groups contains substituents such as listed above for the carbon atoms of the primary amine and aryl (e.g., phenyl) and aralkyl (e.g., benzyl) may also be utilized.

The Pt(II) coordination compounds specified herein do not exist as geometrical isomers; however, the Pt(IV) compounds exist as cis and trans isomers. It is to be further understood that the invention is inclusive of the cis and trans isomers.

The Pt(IV) coordination compounds may also contain two monodentate or one bidentate anionic ligand where only one malonato ligand is present, i.e., where y=1 in the above formula.

Suitable monodentate anionic ligands include chloride, bromide, iodide, nitrite, hydroxide, nitrate, sulfamate, etc. Among the bidentate anionic ligands which may be present are oxalate, pyrophosphate, dithioxalate.

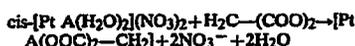
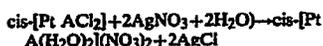
It is to be understood that the invention includes those coordination compounds containing mixed monodentate anionic ligands.

The preferred compounds are those wherein R and R<sub>1</sub> in the above formula are H, methyl or ethyl, i.e., malonatoplatinum, methylmalonatoplatinum and ethylmalonatoplatinum coordination compounds. The most preferred Pt(II) compounds are those malonato-

platinum(II) compounds of the above formula wherein x=1 and R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are each H, i.e., malonatoethylenediamine platinum(II), methylmalonatoethylenediamineplatinum(II) and ethylmalonatoethylenediamineplatinum(II); and wherein x=2 and each R<sub>6</sub> is H, i.e., malonotodiammineplatinum(II), methylmalonotodiammineplatinum(II) and ethylmalonotodiammineplatinum(II).

The preferred Pt(IV) compounds are those wherein x=2, each R<sub>6</sub> is H and y=2, i.e., bismalonato (or bismethylmalonato or bisethylmalonato) diammine platinum(IV).

The coordination compounds of the invention may be prepared by one of a variety of well-known methods. A general method of preparation of the Pt(II) coordination compounds is as follows: Starting compounds having the formula cis-[Pt a(Hal)<sub>2</sub>] wherein Hal is I, Cl or Br and A is one bidentate or two monodentate amine ligands (prepared by the method of S. C. Dhara, Indian J. Chem., Vol. 8, p. 193 (1970)) are reacted with silver nitrate to form the diaquo complex. The latter is then reacted with the malonate ion to form the coordination compounds of the invention. This method is represented by the following reaction scheme:



wherein A is one bidentate amine ligand or two monodentate amine ligands.

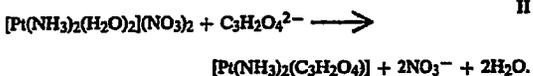
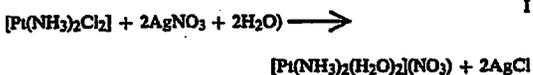
The following non-limiting examples are illustrative of the methods for preparing the compounds of the invention.

#### EXAMPLE 1

##### Malonotodiammineplatinum(II)



Reactions:



Silver nitrate (22.55 g—slightly less than the stoichiometric amount in order to avoid silver contamination) was dissolved in water (50 ml.) and added to [Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>] (20 g) in a 250 ml conical flask. The contents were warmed (60° C.) on a hot plate with rapid stirring until the silver chloride precipitation was complete and the mother liquor was almost colorless. The silver chloride was filtered off using a fine pore sintered glass filter and the precipitate was washed several times with hot water to give a total filtrate volume of 100-200 ml.

Malonic acid (13 g—a twofold excess) was dissolved in water (30 ml) and neutralized with a solution of KOH (~13 g in 30 ml) to pH 5-6. The resulting potassium malonate solution was added to the platinum containing filtrate and the mixture was carefully warmed (to avoid "bumping") on the hot plate until white crystals of the product started to form in great quantity. The mixture was then cooled to room temperature and the product filtered off. The filtrate was reheated for 5-10 minutes and cooled to 0° C. to collect a further crop. The crude yield at this stage was 20.5 g (93%).

The product was recrystallized by dissolving in boiling or near boiling water. The above yield (20.5 g) required about 3 liters of boiling water for complete dissolution. Malonic acid 1 g/L was dissolved in the water to suppress any hydrolysis\*. The filtered solution was cooled to 0° C. to give white fluffy needles (18.25 g—83%).

\*U.V./via spectral and conductivity studies have shown that hydrolysis is negligible.

The crystals decompose between 185°-190°. The structure of the product was verified via an i.r. spectrum. Solubility of the product is low in cold water, i.e., 20 mg/100 mls at 20° C. and 43 mg/100 mls at 37° C., but higher in near boiling water (90°-100° C.)—0.65 g/100 ml.

The empirical composition was verified by elemental analysis:

Malonotodiammineplatinum(II)[Pt(NH<sub>3</sub>)<sub>2</sub>(C<sub>3</sub>H<sub>5</sub>O<sub>4</sub>)]  
Calculated for C<sub>3</sub>H<sub>8</sub>N<sub>2</sub>O<sub>4</sub>Pt.C: 10.88; H: 2.43; N: 8.46; Pt 58.9. Found C: 10.67; H: 2.35; N: 8.54; Pt 58.7.

#### EXAMPLE 2



Silver nitrate (3.64 g) was dissolved in 20 ml of water and added to [Pt(NH<sub>3</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>Cl<sub>2</sub>] (3.5 g) suspended in water (30 ml) in a conical flask. The mixture was stirred on a warm hot plate for 5-10 minutes until all the yellow platinum complex had dissolved to give a yellow liquor plus a copious white silver chloride precipitate. The mixture was filtered through a fine pore filter and the precipitate washed twice with small volumes of hot water. The clear filtrate plus washings was added to an aqueous solution of methylmalonic acid (2 g in 20 mls) which had been adjusted to pH 5-6. The mixture was heated to about 80° C. for five minutes and then cooled to 0° C. The shiny white crystals which formed were filtered and washed with cold water and acetone (Yield 2.65 g). The mother liquor plus aqueous washings was reduced to about half its original volume (~30 mls) to yield a second crop on cooling to 0° C. (Yield 0.85 g). Total Crude yield was 3.50 gms (88%). The complex was recrystallized from a minimum volume of boiling water (around 250 mls) with filtration through a fine pore filter prior to cooling to 0° C. Yield of shiny white leaflets 2.96 g (74%).

Calculated for C<sub>6</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>Pt.C: 19.41 H 3.26 N: 7.55. Found C: 19.11 H 3.61 N: 7.89.

A second crop (0.33 g—8%) was obtained by reducing the bulk of the mother liquor.

#### EXAMPLE 3



Silver nitrate (5.45 g) was dissolved in water (30 ml) and added to trans  $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$  (3 g) suspended in water (30 mls) containing concentrated nitric acid (3 ml). The contents were warmed on a hot plate (70°–80° C.) and stirred for at least one hour. The mixture was filtered through a fine pore sintered glass filter to remove the silver chloride. The precipitate was washed twice with a small volume of hot water. The clear filtrate plus washings was tested with a drop of 1M KCl solutions to determine if excess silver chloride was present. (If the test is positive, sufficient KCl is added dropwise to the bulk solution until no silver chloride is precipitated.) The solution was refiltered and the filtrate reduced to 20–30 mls in volume and cooled to 0° C. to yield plate yellow crystals (presumably trans  $[\text{Pt}(\text{NH}_3)_2(\text{NO}_3)_2]$ ). These were washed with a little cold water and then acetone (Yield 1.8 g). A portion of this yield (1 g) was dissolved in a minimum of hot water to which sodium nitrate (0.2 g) had been added. This solution was filtered into an aqueous solution of malonic acid (0.5 g—a slight excess) which had been adjusted to pH 5–6 with sodium hydroxide. White micro-crystals of the complex quickly form on cooling. These were filtered off and washed with cold water and acetone. (Yield 0.7 g—30–40%).

Calculated for  $\text{C}_6\text{H}_{10}\text{N}_2\text{O}_8\text{Pt}$  C: 16.63 H 2.33 N: 6.47. Found C: 16.60 H 2.64 N: 6.80.

#### GENERAL STRUCTURE CONFORMATION

The malonate group is shown to be coordinated to the platinum by the observed change in the electronic spectra on going from the aquo to the malonate species. Thus, structures such as  $[\text{Pt}(\text{NH}_3)_2(\text{H}_2\text{O})_2]_2(\text{H}_2\text{C}_3\text{O}_4)]$  are ruled out confirming the analytical data. Similarly, zero-time conductivity measurements support a neutral compound. The i.r. spectra show the presence of coordinated carboxyl groups (1600–1650 cm and 1400  $\text{cm}^{-1}$ ) with no  $\text{CO}_2\text{H}$  groups (which would show at 1700–1750 cm). Finally the carboxyl group vibrations are compatible with a chelated structure as compared to oxalate complexes of known structures.

The compounds of the invention were tested for antitumor activity, i.e., for sensitivity to a planar  $\text{dsp}^2$  platinum(II) coordination compound or an octahedral  $\text{d}^2\text{sp}^3$  platinum(IV) coordination compound using our standard screening tumor, solid sarcoma 180 tumor in female Swiss white mice, following standard protocols for this testing as set by the National Cancer Institute. (*Cancer Chemotherapy Rep.*, 25 (1962)).

For these tests an S 180 tumor taken from a sacrificed mouse was dissected free of superfluous tissue and cut under sterile conditions into approximately 10 milligram size pieces. These tissue pieces were then implanted by trocar in the left axillary region, subcutaneously, in new mice. The mice were, on the average, approximately four weeks old and weighed 18–20 grams. Taking day 0 as the day of implant, the animals were sacrificed on day 10. The tumors were excised and weighed and the ratio of the weights of the tumors in mice in the treated animals to the control set of animals was obtained. This ratio, multiplied by 100, is given as the T/C ratio in Table I.

For the first set of tests the coordination compound was freshly dissolved in sterile distilled water and injected intraperitoneally on day 1 into each of the test mice. The volume of the injection was usually  $\frac{1}{2}$  ml. In some cases, in order to get an active dose into the animal where the chemical was not soluble in this amount

of solvent, a fine dispersion was prepared of the dose needed for the test. Thus, some of our test results were obtained on animals where a slurry of the compound was injected. These are so noted in Table I below. In addition, for some of the compounds, there was injected about 1 ml of solution, either in one single injection, or in 2 injections given a few hours apart of  $\frac{1}{2}$  ml each. These injections were initially given in 4 different dose levels for each new compound with 6 mice in each dose level. The tests covered a dose range from a low ineffective dose, to an upper dose level which produced some deaths within the time period of the experiment. The results are set forth in Table I.

TABLE I

Tests of Antitumor Activity (for sensitivity to a planar $\text{dsp}^2$ platinum (II) coordination compound or an octahedral $\text{d}^2\text{sp}^3$ platinum (IV) coordination compound) of Malonate and Substituted Malonate Coordination Complexes of Platinum.						
Tumor-Sarcoma 180 Animal-Female Swiss white mice						
Single injections on days noted, intraperitoneally						
Coordination Complex	Day of Injection	Dose Level	T/C	No. of Deaths		
Malonate-diammineplatinum (II) (slurry in $\text{H}_2\text{O}$ )	1	10 mg/kg	76	0		
		15 mg/kg	38	0		
		20 mg/kg	64	0		
		25 mg/kg	31	0		
		30 mg/kg	7	1/6		
		40 mg/kg	—	6/6		
		50 mg/kg	1	5/6		
		60 mg/kg	—	6/6		
		(solution in $\text{H}_2\text{O}$ )	Daily for days 1–10	4 mg/kg	54	0
				5 mg/kg	56	0
6 mg/kg	23			0		
7 mg/kg	12			0		
30 mg/kg	39			0		
Methylmalonate-diammineplatinum (II) (Solution in $\text{H}_2\text{O}$ )	1	40 mg/kg	26	0		
		50 mg/kg	35	0		
		60 mg/kg	6	0		
		70 mg/kg	124	3/6		
		80 mg/kg	—	6/6		
malonateoethylene-diammineplatinum (II)	1	60	80	0		
		80	138	0		
		100	85	0		
		120	50	0		
		40	72	0		
ethylmalonate-ethylenediamineplatinum (II)	1	60	81	0		
		80	79	0		
		90	47	0		
		100	55	1		
		110	41	0		
		120	58	0		
		45	50	0		
malonate-1,2-propylenediamineplatinum (II)	1	60	9	1		
		75	16	3		
		90	—	5		
		20	69	0		
		40	79	0		
malonate-1,3-propylenediamineplatinum (II)	1	60	21	0		
		80	35	1		
		30 mg/kg	78	0		
		40 mg/kg	80	0		
methylmalonate-ethylenediamineplatinum (II) (solution in $\text{H}_2\text{O}$ )	1	50 mg/kg	51	0		
		60 mg/kg	26	0		
		70 mg/kg	20	1		
		90 mg/kg	4	1		
		30 mg/kg	57	0		
ethylmalonate-diammineplatinum (II) (solution in $\text{H}_2\text{O}$ )	1	40 mg/kg	43	0		
		50 mg/kg	47	0		
		60 mg/kg	39	0		
		70 mg/kg	17	0		
		80 mg/kg	16	0		
		10 mg/kg	88	0		
		20 mg/kg	58	0		
malonateoethylene-diammineplatinum (II) (solution in $\text{H}_2\text{O}$ )	1	40 mg/kg	18	0		
		45 mg/kg	49	0		
		50 mg/kg	35	0		
		55 mg/kg	38	0		
		60 mg/kg	15	3/6		
		80 mg/kg	24	3/6		

TABLE I-continued

Tests of Antitumor Activity (for sensitivity to a planar  $dsp^2$  platinum (II) coordination compound or an octahedral  $d^2sp^3$  platinum (IV) coordination compound) of Malonato and Substituted Malonato Coordination Complexes of Platinum.

Tumor-Sarcoma 180 Animal-Female Swiss white mice  
Single injections on days noted, intraperitoneally

Coordination Complex	Day of Injection	Dose Level	T/C	No. of Deaths
1,1-cyclobutanedicarboxylate diammineplatinum (II)	1	20 mg/kg	71	0
		40 mg/kg	60	0
		60 mg/kg	38	0
		80 mg/kg	42	0
		100 mg/kg	69	0
		120 mg/kg	18	0
		160 mg/kg	62	4
malonatobis (methylamine) platinum (II)	1	80 mg/kg	58	0
		100 mg/kg	53	0
		120 mg/kg	28	0
		140 mg/kg	25	0
		160 mg/kg	17	1
		180 mg/kg	19	1

In addition to the day 1 injections described above, in a number of case injections were delayed until day 8 of tumor growth. In these cases the tumor was usually at least larger than  $\frac{1}{2}$  gm, as estimated by palpation. The animals were then injected and observed for a period of approximately 60 days. Activity was measured by the number of animals whose tumors had regressed to the vanishing point, while still allowing the animal to survive for this time period. Such test results are described in TABLE II below.

TABLE II

Tests of Large Sarcoma 180 Regressions by Malonato Coordination Complexes of Platinum.

Tumor-Sarcoma 180 Animal-Female Swiss white mice  
Single injections on Day 8 intraperitoneally in  $H_2O$  solutions

Coordination Complex	Dose	Total Number of Regressions	Deaths
malonatodiammineplatinum (II)	14 mg/kg	2	4
	16 mg/kg	3	3
	18 mg/kg	4	2
	20 mg/kg	5	1
malonatoethylenediammineplatinum (II)	40 mg/kg	3	3
	45 mg/kg	1	5
	50 mg/kg	2	4
	60 mg/kg	3	3

The results described in Tables I and II indicate that the compounds of the invention are very potent antitumor agents against the S 180 tumor in Swiss white mice.

Confirmatory tests of antitumor activity against the Walker 256 Carcinosarcoma in rats, and the ADJ/P-C6A tumor in mice were conducted. The initial test results are shown in Table III and confirm the potent action of the compounds of the invention against these other tumor systems.

TABLE III

Confirmatory Tests of Antitumor Activity (for sensitivity to a planar  $dsp^2$  platinum (II) coordination compound or an octahedral  $d^2sp^3$  platinum (IV) coordination compound)

Dose	% Inhibition	Deaths
Malonatodiammineplatinum (II)		
Tumor: Walker 256 Carcinosarcoma - Animal - Rat		
Single injection Day 1 in Oil, Intraperitoneally		
10 mg/kg	100	0
20 mg/kg	100	0
40 mg/kg	100	0
80 mg/kg	—	0
Malonatoethylenediammineplatinum (II)		
Tumor: Walker 256 Carcinosarcoma - Animal - Rat		

TABLE III-continued

Confirmatory Tests of Antitumor Activity (for sensitivity to a planar  $dsp^2$  platinum (II) coordination compound or an octahedral  $d^2sp^3$  platinum (IV) coordination compound)

Dose	% Inhibition	Deaths
Single injection Day 1 in Oil, Intraperitoneally		
10	1	0
20	25	0
40	100	0
80	100	0
160	—	all
Tumor: ADJ/PC6A - Animal - Mouse		
Single injection Day 25 in Oil, Intraperitoneally		
4	1.3	0
20	94	0
100	100	0
500	—	all

Samples of the malonato diammine and malonato ethylene diamine complexes of platinum(II) were submitted to the Drug Research and Development Branch of the National Cancer Institute for screening for antitumor activity against the L1210 tumor in mice. The results obtained on this tumor system are shown in Table IV. They confirm the activity of the compounds of the invention.

TABLE IV

Confirmatory Tests of Antitumor Activity (for sensitivity to a planar  $dsp^2$  platinum (II) coordination compound or an octahedral  $d^2sp^3$  platinum (IV) coordination compound) at the National Cancer Institute.

Tumor: L1210 Animal - Mice  
Daily injections Days 1-9, Intraperitoneally

Coordination Complex	Dose	% Increase in Lifespan
Malonatodiammineplatinum (II)	50 mg/kg	163
	25 mg/kg	133
	12.5 mg/kg	115
Malonatoethylenediammineplatinum (II)	50 mg/kg	101
	25 mg/kg	160
	12.5 mg/kg	151
Malonatoethylenediammineplatinum (II) (repeat test)	37.5 mg/kg	121
	25 mg/kg	196
	16.5 mg/kg	160
	11 mg/kg	145

The malonatoplatinum coordination compounds of the invention are preferably dissolved or suspended in water or other pharmaceutically acceptable carrier liquids. The parenterally administrable composition should preferably contain from about 0.5 mg to about 10 mg per ml., it being understood that the amount may vary greatly depending upon the particular compound employed and the animal to be treated.

The platinum coordination compounds of the invention are preferably administered parenterally to an animal affected with a malignant tumor sensitive to a planar  $dsp^2$  platinum(II) coordination compound or an octahedral  $d^2sp^3$  platinum(IV) coordination compound. The duration of treatment and the dose level, of course, will depend in each case upon the size of the host animal, nature and size of the tumor, etc. Generally, however, a dose level of from about 20 to about 200 mg/kg of body weight per day will be sufficient. It is to be understood, however, that the platinum coordination compounds compounded with a suitable pharmaceutical carrier in the same proportions as recited above may also be administered orally at the same dosage levels.

We claim:

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1. A method for treating malignant tumors sensitive to a planar  $d^{sp^2}$  platinum(II) coordination compound or an octahedral  $d^2sp^3$  platinum(IV) coordination compound in animals which comprises parenterally administering to an animal affected with said malignant tumor a solution containing in an amount sufficient to cause regression of the tumor a platinum coordination compound of the formula:



or



wherein:

x=1 or 2;

y=1 or 2;

z=0, 1 or 2, provided that when y=2, z=0, and when y=1, z is greater than 0;

R and R<sub>1</sub> are selected from the group consisting of H, lower alkyl, aryl, aralkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, OH and combine with the carbon atom to form a cycloalkyl or cycloalkenyl group;when x=1, A is HR<sub>2</sub>N-CHR<sub>3</sub>-CHR<sub>4</sub>-NR<sub>5</sub>H and when x=2, A is H<sub>2</sub>NR<sub>6</sub> or an amino acid; wherein R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are the same or different and are selected from the group consisting of H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, hydroxy and lower alkoxy, provided that R<sub>2</sub> and R<sub>5</sub> may also be aryl or aralkyl and each R<sub>6</sub> is the same or different and is selected from the group consisting of H, lower alkyl, aryl, aralkyl, hydroxy lower alkyl, hydroxy- and alkoxy-amines and alkoxy alkyl amines;

when z=1, L is a bidentate anionic ligand, and when z=2, L is a monodentate anionic ligand.

2. A method for treating malignant tumors sensitive to a planar  $d^{sp^2}$  platinum(II) coordination compound or an octahedral  $d^2sp^3$  platinum(IV) coordination compound in animals which comprises orally administering to an animal affected with said malignant tumor a solution containing in an amount sufficient to cause regression of the tumor a platinum coordination compound of the formula:



or



wherein:

x=1 or 2;

y=1 or 2;

z=0, 1 or 2, provided that when y=2, z=0, and when y=1, z is greater than 0;

R and R<sub>1</sub> are selected from the group consisting of H, lower alkyl, aryl, aralkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, OH and combine with the carbon atom to form a cycloalkyl or cycloalkenyl group;when x=1, A is HR<sub>2</sub>N-CHR<sub>3</sub>-CHR<sub>4</sub>-NR<sub>5</sub>H and when x=2, A is H<sub>2</sub>NR<sub>6</sub> or an amino acid; wherein R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are the same or different and are selected from the group consisting of H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, hydroxy and lower alkoxy, provided that R<sub>2</sub> and R<sub>5</sub> may also be aryl or aralkyl and each R<sub>6</sub> is the same or different and is selected from the

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group consisting of H, lower alkyl, aryl, aralkyl, hydroxy lower alkyl, hydroxyl- and alkoxy- amines and alkoxy alkyl amines;

when z=1, L is a bidentate anionic ligand, and

when z=2, L is a monodentate anionic ligand.

3. A composition suitable for parenteral administration to an animal affected with a malignant tumor sensitive to a planar  $d^{sp^2}$  platinum(II) coordination compound or an octahedral  $d^2sp^3$  platinum(IV) coordination compound comprising a pharmaceutically acceptable carrier and a platinum coordination compound of the formula:



or



wherein:

x=1 or 2;

y=1 or 2;

z=0, 1 or 2, provided that when y=2, z=0, and when y=1, z is greater than 0;

R and R<sub>1</sub> are selected from the group consisting of H, lower alkyl, aryl, aralkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, OH and combine with the carbon atom to form a cycloalkyl or cycloalkenyl group;when x=1, A is HR<sub>2</sub>N-CHR<sub>3</sub>-CHR<sub>4</sub>-NR<sub>5</sub>H and when x=2, A is H<sub>2</sub>NR<sub>6</sub> or an amino acid; wherein R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are the same or different and are selected from the group consisting of H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, hydroxy and lower alkoxy, provided that R<sub>2</sub> and R<sub>5</sub> may also be aryl or aralkyl and each R<sub>6</sub> is the same or different and is selected from the group consisting of H, lower alkyl, aryl, aralkyl, hydroxy lower alkyl, hydroxyl- and alkoxy- amines and alkoxy alkyl amines;

when z=1, L is a bidentate anionic ligand, and when z=2, L is a monodentate anionic ligand, said compound being present in an amount sufficient to cause regression of said tumor.

4. A composition suitable for oral administration to an animal affected with a malignant tumor sensitive to a planar  $d^{sp^2}$  platinum(II) coordination compound or an octahedral  $d^2sp^3$  platinum(IV) coordination compound comprising a pharmaceutically acceptable carrier and a platinum coordination compound of the formula:



or



wherein:

x=1 or 2;

y=1 or 2;

z=0, 1 or 2, provided that when y=2, z=0, and when y=1, z is greater than 0;

R and R<sub>1</sub> are selected from the group consisting of H, lower alkyl, aryl, aralkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, OH and combine with the carbon atom to form a cycloalkyl or cycloalkenyl group;when x=1, A is HR<sub>2</sub>N-CHR<sub>3</sub>-CHR<sub>4</sub>-NR<sub>5</sub>H and when x=2, A is H<sub>2</sub>NR<sub>6</sub> or an amino acid; wherein

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R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are the same or different and are selected from the group consisting of H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, hydroxy and lower alkoxy, provided that R<sub>2</sub> and R<sub>5</sub> may also be aryl or aralkyl and each R<sub>6</sub> is the same or different and is selected from the group consisting of H, lower alkyl, aryl, aralkyl,

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hydroxy lower alkyl, hydroxyl- and alkoxy- amines and alkoxy alkyl amines; when z=1, L is a bidentate anionic ligand, and when z=2, L is a monodentate anionic ligand, said compound being present in an amount sufficient to cause regression of said tumor.

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UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 4,657,927

DATED : April 14, 1987

INVENTOR(S) : Michael J. Cleare, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the title page, bracket 62: "Division of Ser. No. 902,706, May 4, 1978, abandoned." should read as --Division of Ser. No. 902,706, May 4, 1978, abandoned which is a divisional of U.S.S.N. 778,955 filed March 18, 1977 now Patent No. 4,140,707 which is a Continuation of U.S.S.N. 260,989 filed June 8, 1972 now abandoned.--

**Signed and Sealed this  
Seventh Day of March, 1989**

*Attest:*

DONALD J. QUIGG

*Attesting Officer*

*Commissioner of Patents and Trademarks*

ORIGINAL FILED

UNITED STATES DISTRICT COURT

JUL 29 2002

FOR THE DISTRICT OF NEW JERSEY

WILLIAM T. WALSH, CLERK

BRISTOL-MYERS SQUIBB COMPANY  
and RESEARCH CORPORATION  
TECHNOLOGIES, INC.,

Plaintiffs,

v.

PHARMACHEMIE B.V.,

Defendant.

CIVIL ACTION No. 01-3751 (MLC)

ENTERED

ON  
THE DOCKET

JUL 29 2002

WILLIAM T. WALSH, CLERK

By LSW  
(Deputy Clerk)

MEMORANDUM OPINION AND ORDER

This matter comes before the Court pursuant to Defendant Pharmachemie B.V.'s ("Pharmachemie") motion for partial summary judgment and Plaintiffs Bristol-Myers Squibb Company's ("BMS") and Research Corporation Technologies, Inc.'s ("RCT") cross-motion for partial summary judgment on the applicability of 35 U.S.C. § 121.<sup>1</sup> The Court has read and considered the memoranda of law and supporting documents submitted by RCT and BMS and Pharmachemie, and on March 4, 2002 the Court heard oral argument on the above issues. At the conclusion of the hearing, the Court ruled in favor of RCT and BMS. This memorandum opinion sets forth the relevant facts and conclusions underlying the Court's decision.

<sup>1</sup> Pharmachemie also moved for summary judgment on the relevant art and the level of skill in the art. RCT and BMS opposed Pharmachemie's motion for partial summary judgment in this regard, but did not cross-move for summary judgment thereon. The Court will defer resolution of these issues until a *Markman* hearing is conducted in order to better understand the nature of the patent-in-suit, the relevant art and the level of skill in the art. Pharmachemie's motion for partial summary judgment on issues of the relevant art is therefore denied without prejudice.

## BACKGROUND

Plaintiffs RCT and BMS filed a complaint in this Court on August 8, 2001 alleging infringement by defendant Pharmachemie of U.S. Patent No. 4,657,927 ("the '927 patent"). RCT is the assignee and BMS is the exclusive licensee of the '927 patent. The claims of the '927 patent are directed to methods of treating tumors with certain platinum-coordination complexes and pharmaceutical compositions containing such platinum-coordination complexes. The '927 patent issued in 1987 and is scheduled to expire in April 2004; it has not been the subject of any prior litigation or patent challenges under the Hatch-Waxman Act.

Pharmachemie filed an Abbreviated New Drug Application ("ANDA") with the U.S. Food and Drug Administration ("FDA") seeking approval to market a powder for injection drug product<sup>2</sup> containing carboplatin, which is a platinum-coordination complex, before the '927 patent expires. The filing of that ANDA forms the basis for this lawsuit pursuant to 35 U.S.C. § 271(e)(2)(A).

Among other defenses, Pharmachemie has asserted that the '927 patent is invalid for obviousness-type double patenting over U.S. Patent No. 4,130,707 ("the '707 patent"). The '707 patent issued on February 20, 1979 and expired on August 24, 1998. The '707 patent stems from the same original application, filed on June 8, 1972, that gave rise to the '927 patent.

Pharmachemie moved for summary judgment that the bar to obviousness-type double patenting contained in 35 U.S.C. § 121 does not apply in this case. In response, RCT and BMS argued that 35 U.S.C. § 121 does apply and precludes Pharmachemie from using the '707 patent as a reference against the '927 patent. Neither party otherwise moved on, and this Court has not considered and does not address, the merits of Pharmachemie's asserted obviousness-type double patenting defense. Because this Court agrees with RCT and BMS that 35 U.S.C. § 121 bars Pharmachemie from using the '707 patent as a reference against the '927 patent, Pharmachemie's obviousness-type double patenting defense is precluded in this case. Pharmachemie's motion is denied, and RCT's and BMS's motion is granted.<sup>3</sup>

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<sup>2</sup> Pharmachemie subsequently filed a second ANDA for an injectable form of carboplatin, and RCT and BMS filed a separate action against Pharmachemie in this district (Case No. 01-CV-1270) with respect to that ANDA. That action has since been consolidated with this case, and this ruling is applicable to both actions.

<sup>3</sup> The parties entered into a Joint Stipulation and Order, effective as of April 22, 2002, that has eliminated certain claims and defenses from this litigation. Due to the stipulations agreed to by the parties and because Section 121 bars Pharmachemie's obviousness-type double patenting defense, only the issue of infringement remains in this case.

## PROSECUTION HISTORY

The facts germane to the applicability of 35 U.S.C. § 121 are principally contained in the prosecution history of the '927 and '707 patents, and these facts are undisputed (though the parties dispute the legal significance of certain facts contained in the prosecution history). A thorough review of the prosecution history is warranted and necessary to determine the applicability of 35 U.S.C. § 121 in this case.

The inventors of the '927 patent-in-suit filed an original patent application on June 8, 1972 (serial number 260,989, "the original '989 application"), containing claims to novel compounds, methods of treatment and pharmaceutical compositions. In its first Office Action, the U.S. Patent and Trademark Office ("PTO") issued a restriction requirement between novel compounds on the one hand and methods of treatment and pharmaceutical compositions on the other. ("Restriction is required . . . between the following inventions: I. Claims 1-8 which are drawn to compounds which is classified in Class 260. II. Claims 9-13 which are drawn to composition and methods of treating cancer which is classified in Class 424." Jan. 11, 1973 Office Action; Ex. A to Cavan Decl. at 2).

The applicants attempted unsuccessfully to traverse the original restriction requirement several times (See, e.g., Feb. 12, 1973 Amendment, Ex. F to Cavan Decl.; July 13, 1973 Amendment, Ex. H to Cavan Decl.) in order to obtain all of their claims in a single patent. After the PTO made "Final" the restriction requirement separating compounds from methods of treatment and pharmaceutical compositions (April 18, 1973 Office Action; Ex. G to Cavan Decl. at 2), the applicants continued to challenge the restriction requirement. (July 13, 1973 Amendment, Ex. H to Cavan Decl.). Because of the restriction requirement, the applicants provisionally elected to pursue initially their compound claims. The applicants prosecuted their compound claims with the PTO but did not immediately obtain allowance for any of their claims.

While an appeal of the rejection of applicants' compound claims was pending with the Board of Patent Appeals, the applicants chose to file a continuation (serial number 778,955, "the '955 continuation"; Ex. Q to Cavan Decl.). After filing the '955 continuation, the applicants abandoned their original '989 application, thus mooted the pending appeal. Because the applicants filed the '955 continuation before abandoning the '989 application, the '955 continuation had the same effect as though filed on the June 8, 1972 priority date of the original '989 application and has the effect in law of continuing the prosecution of that original application. See 35 U.S.C. § 120 and note 4, *infra*.

On August 8, 1977, the PTO mailed its first Office Action on the '955 continuation. Among other things, this Office Action set forth a further restriction requirement, a four-way restriction among groups of compounds. (Ex. R to Cavan Decl. at 2). Examiner Helen Sneed was the PTO Examiner of the '955 continuation. After receiving this Office Action, the applicants submitted an amendment on September 7, 1977, in which they provisionally elected compounds from two of the four groups. (Ex. S to Cavan Decl. at 3-4). After further prosecution, the applicants then received a notice of allowance of their compound claims on April 28, 1978 (Ex. V to Cavan Decl.).

Before the compound claims issued in the '707 patent, the applicants filed a divisional application to their non-elected claims. This divisional application, serial number 902,706 ("the '706 divisional"), was filed on May 4, 1978. In the first Office Action in the '706 divisional, Examiner Sneed (who had examined the '955 continuation) stated that "[r]estriction has been required" between platinum complexes and methods of use and pharmaceutical compositions. (August 17, 1978 Office Action; Ex. Z to Cavan Decl. at 2). The applicants again attempted unsuccessfully to traverse this restriction requirement in an Amendment, dated September 5, 1978 (Ex. AA to Cavan Decl.), so as to obtain claims in categories that were not yet allowed.

After further prosecution, the applicants filed another divisional application, serial number 497,806 ("the '806 divisional"). The '806 divisional was filed on May 25, 1983 (Ex. BB to Cavan Decl.), and a preliminary amendment was filed on June 21, 1983. (Ex. CC to Cavan Decl.). In a first Office Action dated August 3, 1984, the PTO repeated that "Restriction . . . is required under Section 121" between a claim drawn to a platinum complex and claims drawn to methods of use and pharmaceutical compositions. (Ex. DD to Cavan Decl. at 2). After further prosecution, the applicants received a notice of allowance in a June 21, 1985 Office Action for method of treatment and pharmaceutical composition claims. (Ex. EE to Cavan Decl.). The '927 patent issued on April 14, 1987.

#### STANDARD FOR SUMMARY JUDGMENT

Summary judgment is appropriate where there is an absence of a genuine issue of material fact and the moving party is entitled to judgment as a matter of law. Fed.R.Civ.P. 56(c); *Celotex Corp. v. Catrett*, 477 U.S. 317, 327 (1986). When both parties move for summary judgment, the court must evaluate each motion on its own merits, resolving all reasonable inferences against the party whose motion is under consideration. *McKay v. U.S.*, 199 F.3d 1376, 1380 (Fed. Cir. 1999). The question of whether Section 121 applies in this case is a matter of law for the Court. Although material facts are not in dispute, the Court's decision is necessarily premised on the fact-intensive file history of the '927 patent.

#### ANALYSIS OF 35 U.S.C. § 121

The Court grants RCT's and BMS's cross-motion for summary judgment that 35 U.S.C. § 121 applies on the facts of this case to bar Pharmachemie from using the earlier-issued '707 patent as a reference against the '927 patent-in-suit. This decision is based on a careful review of the patent application history in light of the relevant case law.

Section 121 states in pertinent part:

If two or more independent and distinct inventions are claimed in one application, the [PTO] may require the application to be restricted to one of the inventions. If the other invention is made the subject of a divisional application which complies with the requirements of section 120 of this title it shall be entitled to the

benefit of the filing date of the original application. A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application.

35 U.S.C. § 121.

Congress enacted Section 121 as a remedial statute in order to protect applicants and patentees from the unfair consequences of PTO restriction practice. *See, e.g., generally, Applied Materials v. Advanced Semiconductor Materials Am., Inc.*, 98 F.3d 1563, 1568-69 (Fed. Cir. 1996). Prior to the enactment of Section 121, a patentee who had been subjected to a restriction requirement could have its later patent invalidated on the basis of the first issued patent even though the patentee had initially sought to prosecute all of its claims together. *See, e.g., Remington Rand Bus. Serv. v. Acme Card Sys. Co.*, 71 F.2d 628 (4th Cir.), *cert. denied*, 293 U.S. 622 (1934). Section 121 was enacted to eliminate this unfairness, and one of the primary purposes of Section 121 is "to safeguard patent validity from the vagaries of the restriction practice. . . . Section 121 viewed overall, assures that the technicalities of restriction practice are not elevated from their purpose of examination convenience to a potential taint on the validity of ensuing patents." *Applied Materials* at 1568-69; *see also* S. Rep. No. 82-1979 (June 27, 1952), *reprinted in* 1952 U.S.C.C.A.N. 2394, 2413.

In this case, the first patent (the '707 patent) "issu[ed] on an application with respect to which a requirement for restriction [was] made."<sup>4</sup> From a review of the prosecution history as a whole, it is evident that the original 1973 restriction requirement remained in effect and required the applicants to pursue their method of treatment and pharmaceutical composition claims in a divisional application. This restriction requirement was never cancelled, revoked or withdrawn. Pharmachemie has not offered any persuasive authority in support of its contention that the 1973 restriction requirement was either explicitly or implicitly withdrawn by the PTO's further

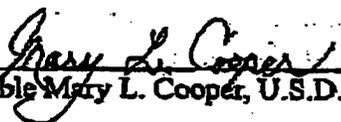
<sup>4</sup> This is true for at least the reason that the '955 continuation together with the original '989 application constitute "one continuous application, within the meaning of the law." *Godfrey v. Eames*, 68 U.S. 317, 325-26 (1863); *see also Transco Prods. Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 556-57 (Fed. Cir. 1994) (citing to *Godfrey*) ("Before section 120 was enacted, the Supreme Court noted that a continuing application and the application on which it is based are considered part of the same transaction constituting one continuing application . . . . The legislative history of section 120 does not indicate any congressional intent to alter the Supreme Court's interpretation of continuing application practice."), *cert. denied*, 513 U.S. 1151 (1995).

restriction requirement in the '955 continuation, and Pharmachemie's argument is belied by the whole of the prosecution history. Examiner's Sneed's comments in the first Office Action on the '706 divisional corroborate that the restriction between compounds and methods of treatment and pharmaceutical compositions remained in effect through the '955 continuation. ("Restriction . . . has been required" between two claims drawn to compounds and claims "drafted to composition[s] and method[s]"; Ex. Z to Cavan Decl. at 2). On at least four other occasions, the PTO reiterated that applicants' compound claims needed to be separated from their method of treatment and pharmaceutical composition claims.<sup>5</sup> The Court concludes that the divisional application pursuing method of treatment and pharmaceutical composition claims was filed as a result of the restriction requirement and was not a "voluntary" act; over the years, the applicants made repeated attempts to traverse the PTO's restriction requirement but were not permitted to combine compound claims with method of treatment and pharmaceutical composition claims.

Further, the '927 patent is fully consonant with the 1973 restriction requirement relied upon by applicants, as the claims of the '927 patent do not cross back over the line of demarcation to claim subject matter claimed in the earlier-issued '707 patent. The '707 patent contained claims drawn exclusively to compounds, and the '927 patent-in-suit contains claims drawn exclusively to methods of treatment and pharmaceutical compositions. Thus, the consonance requirement as set forth in *Gerber Garment Tech., Inc. v. Lectra Sys., Inc.*, 916 F.2d 683 (Fed. Cir. 1990), is met here.

Finally, the cases upon which Pharmachemie has relied do not militate in favor of a contrary decision by this Court. The Court of Customs and Patents Appeals' decisions in *In re Ziegler*, 443 F.2d 1211 (C.C.P.A. 1971) (involving the *official withdrawal* of a restriction requirement in a parent application), *In re Wright*, 393 F.2d 1001 (C.C.P.A. 1968) (no PTO imposed restriction requirement) and *In re Schneller*, 397 F.2d 350 (C.C.P.A. 1968) (same), do not change the Court's conclusion that Section 121 applies in this case.

Here, the PTO unequivocally imposed a restriction requirement separating the applicants' compound claims from their method of treatment and pharmaceutical composition claims, it never rescinded that requirement, and two patents then issued (one with claims drawn exclusively to compounds and one with claims drawn exclusively to methods of treatment and pharmaceutical compositions). Section 121 applies in this case to bar the use of the earlier-issued '707 patent as a reference against the later-issued '927 patent-in-suit.

  
Honorable Mary L. Cooper, U.S.D.J.

<sup>5</sup> See, e.g., January 11, 1973 Office Action (Ex. E to Cavan Decl.); April 18, 1973 Office Action (Ex. G to Cavan Decl.); March 22, 1974 Office Action (Ex. I to Cavan Decl.); and August 3, 1984 Office Action (Ex. DD to Cavan Decl.).

**RIDER****28 U.S.C. § 1292(b) Certification**

Pharmachemie has requested certification so that it may appeal this decision on an interlocutory basis. RCT and BMS do not join in Pharmachemie's request, but they have agreed not to oppose this Court's certification of an interlocutory appeal. I hereby permit Pharmachemie to appeal this ruling on an interlocutory basis, finding that this case "involves a controlling question of law as to which there is substantial ground for difference of opinion and that an immediate appeal from an order may materially advance the ultimate termination of the litigation." 28 U.S.C. § 1292(b). I hereby certify the following question for interlocutory review by the United States Court of Appeals for the Federal Circuit.

**CERTIFIED QUESTION**

Where (i) the PTO found that two or more independent and distinct inventions were claimed in one application ("original application"), and the PTO required the original application to be restricted to one of the inventions ("first restriction requirement"); (ii) the earlier-issued patent issued from a continuation of the original application; (iii) before issuance of the earlier-issued patent, the other invention was made the subject of a divisional application which ultimately matured into the later-issued patent ("divisional application"); (iv) the first restriction requirement was never canceled, revoked, or withdrawn; and (v) a restriction requirement was imposed by the PTO during prosecution of the divisional application ("later restriction requirement"),

Did the District Court err in holding that 35 U.S.C. § 121 applies in this case to bar the use of the earlier-issued '707 patent as a reference against the later-issued '927 patent-in-suit, based upon the following legal rulings:

- (1) The divisional application was filed "as a result of" the first restriction requirement, within the meaning of Section 121;
- (2) The PTO did not explicitly or implicitly withdraw the first restriction requirement by imposing the later restriction requirement, and therefore the first restriction requirement continued to apply to the divisional application for purposes of invoking Section 121; and
- (3) The claims of the earlier-issued patent and the claims of the later-issued patent are fully consonant with the first restriction requirement?

SO ORDERED:

  
MARY L. COOPER, U.S.D.J.

JULY 25, 2002

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 Trenton, NJ 08607  
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 Attorneys for Defendant  
 Pharmachemie B.V.

**ORIGINAL FILED**

**OCT 25 2002**

**WILLIAM T. WALSH, CLERK**

**UNITED STATES DISTRICT COURT  
 FOR THE DISTRICT OF NEW JERSEY**

**BRISTOL-MYERS SQUIBB  
 COMPANY and  
 RESEARCH CORPORATION  
 TECHNOLOGIES, INC.,**

**Plaintiffs,**

**v.**

**PHARMACHEMIE B.V.,  
 Defendant.**

**CIVIL ACTION No. 01-3751 (MLC)  
 (Civil Action No. 02-1270  
 consolidated herewith)**

**ENTERED**

**on**

**THE DOCKET**

**on 10/28/02  
 WILLIAM T. WALSH, CLERK**

*Handwritten signature*

**FINAL JUDGMENT**

**WHEREAS,** on July 29, 2002 this Court issued a Memorandum Opinion and Order granting summary judgment for plaintiffs on the invalidity defense of obviousness-type double patenting on the grounds that 35 U.S.C. § 121 barred use of U.S. Patent No. 4,140,707 (the "707 patent") as a reference against U.S. Patent No. 4,657,927 (the "927 patent").

**WHEREAS,** on October 2, 2002 the United States Court of Appeals for the Federal Circuit denied defendant Pharmachemie B.V.'s ("Pharmachemie") petition to file an interlocutory appeal from the Court's summary judgment order.

**WHEREAS,** the only issue remaining in this case is the issue of infringement.

WHEREAS, Pharmachemie, in order to establish its right to appeal the § 121 bar issues, has, with the written consent of plaintiffs, filed an Amended Answer and Counterclaim admitting that Pharmachemie's filing of the ANDAs referenced in the consolidated complaint is an act of infringement of at least one claim of the '927 patent and withdrawing its affirmative defense of non-infringement.

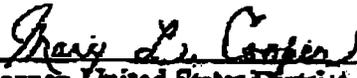
WHEREAS, now that the Amended Answer and Counterclaim has been filed, no issues remain to be tried.

WHEREFORE, final judgment be and hereby is entered as follows:

1. Judgment is in favor of plaintiffs Research Corporation Technologies, Inc. and Bristol-Myers Squibb Company on their Consolidated Amended Complaint and against defendant Pharmachemie B.V. on its Counterclaims in that U.S. Patent No. 4,657,927 is not invalid (and, therefore, not unenforceable as a result), Pharmachemie's filing of the Abbreviated New Drug Applications for carboplatin products is an act of infringement of at least one claim of that patent pursuant to 35 U.S.C. § 271(e)(2), and that the manufacture, use, sale, or offer for sale within the United States, or importation into the United States, of the carboplatin products referred to in the Abbreviated New Drug Applications would infringe at least one claim of that patent.

2. It is further ordered that the effective date of approval of Pharmachemie's Abbreviated New Drug Application Nos. 76-162 and 76-292 is determined to be the date on which any Food and Drug Administration exclusivity that may be granted to plaintiffs pursuant to 21 U.S.C. Section 355a expires, said exclusivity coming into effect upon the expiration of the '927 patent, and, if no such exclusivity is granted, a date not earlier than the April 14, 2004 expiration of the '927 patent.

3. It is further ordered that, prior to the effective date of approval of Pharmachemie's Abbreviated New Drug Application Nos. 76-162 and 76-292, defendant Pharmachemie is enjoined from commercially manufacturing, using, selling or offering for sale within the United States, or importing into the United States, the carboplatin products referred to in those Abbreviated New Drug Applications other than for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs as set forth in 35 U.S.C. Section 271(e)(1).

  
Mary L. Cooper, United States District Judge

Dated: October 22, 2002

**United States Court of Appeals for the Federal Circuit**

03-1077

BRISTOL-MYERS SQUIBB COMPANY,

Plaintiff-Appellee,

and

RESEARCH CORPORATION TECHNOLOGIES, INC.,

Plaintiff-Appellee,

v.

PHARMACHEMIE B.V.,

Defendant-Appellant.

David T. Pritikin, Sidley Austin Brown & Wood, of Chicago, Illinois, argued for both plaintiffs-appellees. With him on the brief were Constantine L. Trela, Jr., Lisa A. Schneider, and Marc A. Cavan; and Eugenia S. Hansen, Sidley Austin Brown & Wood, of Dallas, Texas. On the brief for plaintiff-appellee Bristol-Myers Squibb Company, was Robert L. Baechtold, Fitzpatrick, Cella, Harper & Scinto, of New York, New York.

Francis C. Lynch, Palmer & Dodge, LLP of Boston, Massachusetts, argued for defendant-appellant. With him on the brief was Laurie S. Gill.

Appealed from: United States District Court for the District of New Jersey

Judge Mary L. Cooper

# United States Court of Appeals for the Federal Circuit

03-1077

BRISTOL-MYERS SQUIBB COMPANY,

Plaintiff-Appellee,

and

RESEARCH CORPORATION TECHNOLOGIES, INC.,

Plaintiff-Appellee,

v.

PHARMACHEMIE B.V.,

Defendant-Appellant.

---

DECIDED: March 17, 2004

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Before NEWMAN, MICHEL, and BRYSON, Circuit Judges.

Opinion for the court filed by BRYSON, Circuit Judge. Dissenting opinion filed by NEWMAN, Circuit Judge.

BRYSON, Circuit Judge.

The question in this patent case is whether the patent in suit is invalid for double patenting. The district court held on summary judgment that an earlier patent, which stemmed from the same application as the patent in suit, could not be used as a reference against the patent in suit for double patenting purposes. Bristol-Myers Squibb Co. v. Pharmachemie, B.V., No. 01-3751 (MLC) (D.N.J. July 29, 2002).

Because we disagree with a key conclusion on which the district court's summary judgment was based, we vacate the district court's judgment and remand the case to the district court for further proceedings.

I  
A

Research Corporation Technologies, Inc., is the owner of U.S. Patent No. 4,657,927 ("the '927 patent"), and Bristol-Myers Squibb Co. is the exclusive licensee under that patent. The patent claims (1) methods for treating malignant tumors with certain platinum coordination compounds and (2) compositions containing those compounds in amounts sufficient to cause regression of those tumors. Appellant Pharmachemie, B.V., filed an Abbreviated New Drug Application ("ANDA") with the Food and Drug Administration, seeking FDA approval to market a cancer-treating drug covered by the '927 patent. Research Corporation Technologies, Inc., and Bristol-Myers Squibb Co. (collectively "Bristol-Myers") brought suit charging Pharmachemie with patent infringement under 35 U.S.C. § 271(e)(2). As a defense, Pharmachemie asserted that the '927 patent was invalid for obviousness-type double patenting over U.S. Patent No. 4,140,707 ("the '707 patent"), which was issued in 1979 and expired in 1998.

B

The double patenting issue in this case turns on whether Bristol-Myers is entitled to invoke section 121 of the Patent Act, 35 U.S.C. § 121, as a defense against the claim of double patenting. That issue in turn depends on an interpretation of the prosecution history of the '707 and '927 patents.

The '927 patent can be traced to an application filed with the Patent and Trademark Office in 1972. That application, Serial No. 260,989 ("the '989 application"), disclosed and claimed compounds corresponding generally to the compounds that were ultimately claimed in the '707 patent. In addition, the '989 application claimed methods of treatment and compositions corresponding to the claims that were ultimately included in the '927 patent.

In the course of the prosecution of the '989 application, the examiners imposed two restriction requirements. The first, imposed in 1973, required that the applicants elect either the compound claims, classified in art class 260, or the method of treatment and composition claims, classified in art class 424. In addition, the 1973 restriction requirement directed the applicants to elect "a single disclosed species for examination on the merits." As a result of the 1973 restriction requirement, the applicants elected the compound claims and withdrew the non-elected method of use and composition claims from further consideration at that time. The examiner then rejected the elected compound claims on the basis of lack of utility.

In 1974, a different examiner issued a second restriction requirement on the '989 application. That restriction requirement identified four different compound groups within the compounds claimed in the application as constituting independent and distinct inventions. The four groups were: (1) "Organometallic platinum compound[s] classified in class 260, subclass 429"; (2) "Platinum compounds containing 'heterocyclic amines' or [']heterocyclic substituents' classified in class 260, subclass 270R and many various subclasses"; (3) "Compounds of the above type with 2-valent platinum and no L moiety"; and (4) "Compounds with 4-valent platinum containing various 'anionic'

ligands.” In addition, the examiner expressly stated that the 1973 restriction requirement segregating the compound claims from the method of use and composition claims was maintained. The applicants did not file a divisional application in response to either of the restriction requirements, but instead appealed the final rejection of the claims to the PTO Board of Appeals.

In 1977, while that appeal was pending, the applicants filed a continuation application, Serial No. 778,955 (“the ‘955 application”), and abandoned the ‘989 application. The ‘955 application presented all of the original claims of the ‘989 application for examination. A new examiner examined the ‘955 application “for restriction only” and imposed a new restriction requirement. The 1977 restriction requirement differed from the 1973 and 1974 requirements that had been imposed in connection with the ‘989 application. The 1977 restriction requirement mandated that the claims be separated into four groups, but unlike the 1973 restriction requirement, it did not segregate the compound claims from the method of use and composition claims. Instead, the first two of the four groups set forth in the restriction requirement referred to art groups that included methods of use and compositions as well as compounds. The first group consisted of “[o]rganometallic platinum compound[s] classified in class 260, subclass 429 [compounds] and class 424, subclass 287 [methods of use and compositions].” The second group consisted of “[p]latinum compounds containing ‘heterocyclic amines’ or [‘]heterocyclic substituents’ classified in Class 260, subclasses 270R and many various subclasses [compounds], and Class 424 subclass 245 [compositions and methods of use].” The third group set forth in the 1977 restriction requirement consisted of “[c]ompounds of the above type with 2-valent

platinum and no L moiety." The fourth group consisted of "[c]ompounds with 4-valent platinum containing various 'anionic' ligands."

The applicants responded to the 1977 restriction requirement by electing four claims, which corresponded to the claims that were ultimately included in the '707 patent that issued two years later. Before that patent issued, however, the applicants filed a divisional application, Serial No. 902,706 ("the '706 divisional application"). After a preliminary amendment, the '706 divisional application included 16 claims, denominated claims 5-20. Claims 5-13 were cancelled shortly thereafter. The remaining claims, in slightly rewritten form, claimed the non-elected compound groups and the methods of use and compositions originally claimed in both the '989 and the '955 applications. Following the filing of the '706 divisional application, the '707 patent issued, containing the four compound claims that had been elected from the '955 application.

The examiner issued a restriction requirement with respect to the '706 divisional application. The office action began with the statement "Restriction has been required . . . between the following inventions," after which the examiner divided the claims into three groups: claim 14, "which is drawn to Platinum (II) complexes classified in Class 260, subclass 270R"; claim 15, "which is directed to platinum (IV) complexes classified in Class 260, subclass 429R"; and claims 16-20, "which are drafted to composition and method [sic] classified in Class 424, subclass 245, 287." In the same office action, the examiner then set forth a second, four-way restriction requirement, which replicated the four-way restriction requirement that had earlier been imposed on the claims of the '955 application. The applicants responded to that office action by

asserting that the two restriction requirements seemed to be "somewhat in conflict" in that "any invention elected in accordance with the requirements [of the first] would necessarily involve election of one or more of the groups set forth [in the second]." In an effort to comply with the requirements, however, the applicants elected claim 14 of the '706 divisional application.

In 1983, after further unsuccessful appellate proceedings, the applicants filed another divisional application, which again consisted of the original 1972 application. In preliminary amendments, the applicants canceled the 13 original claims and added, as claims 14-19, the claims that had been claims 15-20 of the '706 divisional application. Another examiner was assigned to the application and another restriction requirement was issued. This time, the examiner divided the claims into two groups, one consisting of claim 14, "drawn to platinum IV complexes, classified in Class 260, subclass 239E," and the other consisting of claims 15-19, "drawn to methods of use and compositions, classified in Class 424, subclass 245." In 1987, that application matured into the '927 patent. The four claims of the '927 patent corresponded generally to four of the method of use and composition claims of the 1983 divisional application.

### C

The district court noted that the question whether section 121 of the Patent Act is available to Bristol-Myers depends on whether the applicants were required by a restriction requirement to prosecute the claims that ultimately became part of the '927 patent separately from the claims that became part of the '707 patent. The court concluded that the statutory requirement was satisfied because "it is evident that the original 1973 restriction requirement remained in effect and required the applicants to

pursue their method of treatment and pharmaceutical composition claims in a divisional application. This restriction requirement was never cancelled, revoked, or withdrawn.”

Accordingly, the court concluded,

the divisional application pursuing method of treatment and pharmaceutical composition claims was filed as a result of the restriction requirement and was not a “voluntary” act; over the years, the applicants made repeated attempts to traverse the PTO’s restriction requirement but were not permitted to combine compound claims with method of treatment and composition claims.

Because the court concluded that section 121 barred the assertion of double patenting as a basis for Pharmachemie to assert the invalidity of the '927 patent, and because Pharmachemie abandoned any other defense against Bristol-Myers’ claim of infringement, the court entered final judgment of infringement. Pharmachemie appealed.

## II

Section 121 of the Patent Act provides, in pertinent part, as follows:

If two or more independent and distinct inventions are claimed in one application, the Director may require the application to be restricted to one of the inventions. If the other invention is made the subject of a divisional application which complies with the requirements of section 120 [of the Patent Act] it shall be entitled to the benefit of the filing date of the original application. A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application.

35 U.S.C. § 121.

As section 121 has been interpreted by this court, Bristol-Myers is entitled to invoke the statutory prohibition against the use of the '707 patent "as a reference" against the divisional application that resulted in the '927 patent only if the divisional application was filed as a result of a restriction requirement and is consonant with that restriction requirement. See Geneva Pharms., Inc. v. Glaxosmithkline PLC, 349 F.3d 1373, 1378, 1381 (Fed. Cir. 2003); Gerber Garment Tech., Inc. v. Lectra Sys., Inc., 916 F.2d 683, 687 (Fed. Cir. 1990). The district court held that the divisional application that led to the '927 patent was filed as a result of, and was consistent with, the restriction requirement issued in 1973. According to the court, that 1973 restriction requirement resulted in the 1978 divisional application that ultimately resulted in the '927 patent, because the 1973 restriction requirement "remained in effect and required the applicants to pursue their method of treatment and pharmaceutical composition claims in a divisional application." Although the 1973 restriction requirement was issued against the '989 application, and not against the '955 application, from which the 1978 divisional was filed, the court ruled that the 1973 restriction requirement applied to the later application because it "was never cancelled, revoked, or withdrawn."

Our review of the district court's summary judgment order in this factually complex case presents a relatively straightforward question: whether the district court was correct to conclude, as a matter of law, that the 1973 restriction requirement was applicable to the 1977 application and therefore resulted in the 1978 divisional application.<sup>1</sup> The district court held that it was and that the patent therefore cannot be

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<sup>1</sup> The dissent appears to take the position that by issuing the '927 patent the PTO in effect found that the applicant complied with all applicable restriction requirements, and that we should not disturb that determination. In fact, however, the question

cited as a reference against the '927 patent for double patenting purposes. Pharmachemie, on the other hand, argues that the 1973 restriction requirement was not in effect at the time of the filing of the divisional application that matured into the '927 patent, and that the '927 patent therefore cannot be said to have been filed as a result of that restriction requirement.

We agree with Pharmachemie. The '955 continuation application, which was filed in 1977, began a new proceeding in which all of the original claims of the '989 application were once again presented for examination.<sup>2</sup> In 1977, when the examiner for the '955 application issued the restriction requirement for that application, she did not reinstate or even advert to the 1973 restriction requirement. In fact, the 1977 restriction requirement that she issued at the outset of the prosecution of the '955

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whether the requirements of section 121 have been satisfied is a question of law that we have addressed de novo after reviewing the relevant materials. See Geneva, 349 F.3d at 1377; In re Berg, 140 F.3d 1428, 1432 (Fed. Cir. 1988). The approach suggested by the dissent would be inconsistent with the approach we have employed in similar cases in the past. In Geneva, and Gerber, for example, we held that applicants had failed to satisfy the requirements of section 121 based on our analysis of the prosecution history. Even in cases in which we have held that the requirements of section 121 were satisfied, we did so not as a result of deference to the PTO but as a result of our own analysis of the prosecution history. See Symbol Techs., Inc. v. Opticon, Inc., 935 F.2d 1569 (Fed. Cir. 1991); Tex. Instruments Inc. v. U.S. Int'l Trade Comm'n, 988 F.2d 1165 (Fed. Cir. 1993).

<sup>2</sup> Bristol-Myers has not cited any statutory or regulatory basis for concluding that the 1973 restriction requirement was automatically applicable to the '955 continuation. Bristol-Myers cites several cases and a provision (section 201.07) of the 1972 version of the Manual of Patent Examining Procedure ("MPEP") for the proposition that a continuation application and its parent are "one continuous application, within the meaning of the law." Godfrey v. Eames, 68 U.S. 317, 326 (1864); accord Transco Prods. Inc. v. Performance Contracting, Inc., 38 F.3d 551, 556-57 (Fed. Cir. 1994). Those authorities, however, do not support the proposition for which Bristol-Myers cites them. The cases deal only with the issue of priority, and not with PTO procedure for examining a continuation application in light of its parent. Likewise, the cited MPEP

application was different from, and inconsistent with, the 1973 restriction requirement. The 1977 restriction requirement, unlike the 1973 restriction requirement, grouped compounds together with methods of use and compositions in at least two of the four invention groups, while the 1973 restriction requirement directed that compounds be segregated from methods of use and compositions. Moreover, the examiner examined the method of use and composition claims "for subject matter of [the elected groups] readable on the elected species" as reflected in the subsequent office action. This suggests that the applicant could have complied with the 1977 restriction requirement in a way that would have been contrary to the categories set forth in the 1973 restriction requirement. By imposition of a new and different restriction requirement and failing to make any reference to the restriction requirements imposed in connection with the parent application, the examiner made clear that the previous restriction requirements did not carry over to the '955 application.

Bristol-Myers argues that the examiner in effect adopted the 1973 restriction requirement in the course of the prosecution of the '955 application. Bristol-Myers suggests that the four-way restriction requirement of 1977 incorporated the two-way restriction requirement of 1973 and thus resulted in a six- or eight-way restriction requirement, part explicit and part implicit. There is no indication in the record, however, that the PTO intended one of the two restriction requirements imposed on the '89 application to carry forward to the '955 application, but not the other. Moreover, the record does not indicate that the applicant proceeded under the assumption that the 1973 restriction requirement continued in effect. During prosecution of the '706

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section does not address PTO procedure for examining a continuation, but merely sets

divisional application, when a restriction requirement similar to the 1973 requirement appeared in conjunction with a restriction requirement similar to the 1977 restriction requirement, the applicant noted that the two requirements were "somewhat in conflict" and that "any invention elected in accordance with the requirements [of the first] would necessarily involve election of one or more of the groups set forth [in the second]."

There was, to say the least, some confusion at various points as to how the various claims should be sorted out for purposes of restriction. But even though at some points restriction requirements were imposed that were similar to, or even identical to, earlier restriction requirements, each requirement was nevertheless separately imposed with respect to each separate application. The record thus does not support the inference that any of the various restriction requirements automatically carried forward, in part or in whole, from one application to the next.<sup>3</sup> For that reason, we cannot sustain the district court's summary judgment order, which was based on the court's conclusion that the 1973 restriction requirement continued in effect with respect to the continuation application that was filed in 1977. Accordingly, we reverse the district court's judgment and remand for further proceedings.

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forth the requirements of a continuation application.

<sup>3</sup> Pointing to the examiner's statement, in an office action on the '706 divisional application, that restriction "has been required" between three categories of inventions, Bristol-Myers argues that the statement indicates the examiner considered that at least some of the restriction requirements from previous applications continued to apply to the later applications. We do not agree with Bristol-Myers' conclusion in that regard. The examiner's isolated use of the present perfect tense in the 1978 office action is not a sufficient basis from which to infer that the examiner understood, or intended to convey, that a restriction requirement imposed five years earlier, in connection with a grandparent application, continued to be in effect for all applications related to the original '989 application because it was never formally withdrawn.

In light of the complexity of the factual record in this case, we go no further than to address the ground on which the district court ruled. Whether further analysis of the sequence of applications, restriction requirements, and responses by the applicants may reveal other grounds for concluding that the protection of section 121 should be extended to some or all of the claims of the '927 patent is a matter for the district court to address in the first instance.

VACATED and REMANDED.

# United States Court of Appeals for the Federal Circuit

03-1077

BRISTOL-MYERS SQUIBB COMPANY,

Plaintiff-Appellee,

and

RESEARCH CORPORATION TECHNOLOGIES, INC.,

Plaintiff-Appellee,

v.

PHARMACHEMIE B.V.,

Defendant-Appellant.

NEWMAN, Circuit Judge, dissenting.

My colleagues have peered deep into the recesses of patent examination, plucked out a routine and unreviewable administrative procedure -- the "restriction requirement" for facilitating examination of complex cases -- and created a new standard of administrative review and a new ground of patent invalidity. I must, respectfully, dissent.

Whether or not the patent applicant here in suit was given proper or consistent restriction requirements by the various examiners, the issuance of these actions was entirely discretionary with the Commissioner. When the examiners accepted the

applicant's elections and the divisional applications filed in compliance therewith, these actions are not rulings of law; they are discretionary actions reviewable, if at all, under the strictures of the Administrative Procedure Act. It is not disputed that the applicant made the required election for each restriction requirement, and that the divisional and continuing applications at issue were accepted by the examiner as properly filed. The district court reviewed these procedures and found that 35 U.S.C. §121 protected the patentee from citation of the earlier patent against the later one:

35 U.S.C. §121. . . . A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them . . . .

Thus the district court held that under 35 U.S.C. §121 the patent at issue was not an available reference.

If my colleagues on this panel now intend to require that the minutiae of the various discretionary restriction requirements and the acceptance by the examiners of the applicant's compliances with those requirements are subject to appellate review, the standard of review is that of the Administrative Procedure Act, not the de novo untangling of internal procedures for which my colleagues remand to the district court.

See Dickinson v. Zurko, 527 U.S. 150 (1999).<sup>1</sup>

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<sup>1</sup> The majority opinion, in its footnote 1, misperceives my concern. The issue is not the standard of review of the agency's findings of substantive fact in determining patentability. In holding that "the PTO is an 'agency' subject to the APA's constraints," Zurko, 527 U.S. at 1819, the Court required that matters of agency procedure (such as whether a restriction requirement must be repeated) are delegated to the agency. The APA assigns such procedures, which have no substantive impact, to internal agency management; the panel majority distorts the administrative process

## Restriction Requirements are not Appealable within the PTO

The PTO has myriad procedures to guide and facilitate the conduct of patent examination. Rules of operation are essential to the effective performance of a complex agency with many employees and an enormous volume of work.<sup>2</sup> The PTO's patent examination procedures fill a three-inch thick Manual of fine print. In addition, PTO regulations fill Volume 37 of the Code of Federal Regulations. Over 3500 scientists and engineers apply these procedures to the most advanced science and technology of the age.

Early in the evolution of patent examination the Patent Office adopted the discretionary "restriction" practice, to simplify the search and examination of complex inventions. In electing to require "restriction" the patent examiner requires the applicant to select a specified aspect of the claimed subject matter, the examiner having first divided the subject matter into groups of claims based on classification for search purposes. The applicant then selects the aspect to be examined, and usually also "traverses" the requirement, a formality grounded in administrative protocols. Examination then proceeds as to the selected subject matter. The non-selected aspects are then removed from consideration in that case; they may be rejoined or they may be moved into one or more divisional applications for examination. Lest the first patent be citable as prior art against a divisional application -- an illogical event that

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in holding that the agency's examining practices in complex cases receive plenary judicial review and management.

<sup>2</sup> In 2002 the PTO received 333,688 new patent applications and granted 162,221 patents. See 2002 United States Patent & Trademark Office Performance & Accountability Rep. at 15. The average pendency was twenty-four months, id., and hundreds of thousands of applications are under examination at any given time.

apparently had occurred -- the 1952 Patent Act precluded this event by enacting §121. Thus the patentee was shielded from this unintended substantive consequence of an examination procedural convenience. In Applied Materials, Inc. v. Advanced Semiconductor Materials America, Inc., 98 F.3d 1563 (Fed. Cir. 1996) this court explained:

The purpose of §121 is to accommodate administrative convenience and to protect the patentee from technical flaws based on this unappealable examination practice . . . . Section 121, viewed overall, assures that the technicalities of restriction practice are not elevated from their purpose of examination convenience to a potential taint on the validity of the ensuing patents.

Id. at 1568.

In the present case, four different examiners imposed somewhat variant restriction requirements, reflecting their divergent views of how the subject matter should be divided for search and examination. Some examiners grouped all of the platinum compounds together and all of the cancer-treatment uses together; another put the compositions with the compounds, another with the uses; another separated the different kinds of platinum compounds; another included the corresponding composition and use claims with each type of platinum compound. Some required an election of species; some did not.

To each examiner's restriction requirement, the applicant made the requisite election from among the examiner's categories, while duly "traversing" the requirement. None of the examiners objected to the applicant's compliance with any of the restriction requirements. None rejected a later filed application on an earlier one. None of these actions is appealable to the Board of Appeals or the courts. The Court of Customs and Patent Appeals explained that a restriction decision is not an actual rejection on

grounds of patentability, but simply a procedural requirement. The court explained in In re Hengehold, 440 F.2d 1395, 1399 (CCPA 1971):

On considering §§121, 132 and 134 and the intent unmistakably evinced by the clear language therein, it is evident to us that Congress . . . decided not to regard the procedure involved in matters of "division" or "restriction" as a "rejection." Instead, section 121 denominates restriction procedure as a "requirement." . . . It is apparent, then, that Congress intended to differentiate between whatever requirements and objections an examiner might make on the one hand, and matters involving actual rejections of claims on the other, at least insofar as its provision of statutory rights of appeal to the board accruing from such actions in and of themselves.

440 F.2d at 1402-03 (citations omitted). Restriction requirements are like other PTO "requirements" that are "matters of a discretionary, procedural or nonsubstantive nature." Id. at 1403. See also In re Harnisch, 631 F.2d 716 (CCPA 1980):

In the PTO, patent applications are examined for compliance with the statutory provisions of Title 35, United States Code, as set forth in sections 100, 101, 102, 103, and 112. These are considered to be examinations "on the merits." There are also procedural questions arising under section 121 and related PTO rules concerned with "restriction practice."

Id. at 721.

The only remedy available to an applicant who is dissatisfied with the restriction requirement is a petition to the Director for review:

37 C.F.R. §1.144. After a final requirement for restriction, the applicant, in addition to making any reply due on the remainder of the action, may petition the Director to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested (see §1.181).

Such a procedure implements standard administrative practice relative to agency actions. See generally Martin v. Occupational Safety & Health Review Comm'n, 499 U.S. 144, 151 (1991) ("Because applying an agency's regulation to complex or

changing circumstances, calls upon the agency's unique expertise and policymaking prerogatives, we presume that the power authoritatively to interpret its own regulations is a component of the agency's delegated lawmaking powers.").

Indeed, should there be any imperfections in the agency's interpretations or applications of the regulations with respect to the examiner's theory of restriction or compliance by the applicant, they are not grounds of invalidity. See Magnivision, Inc. v. Bonneau Co., 115 F.3d 956 (Fed. Cir. 1997):

Procedural lapses during examination, should they occur, do not provide grounds of invalidity. Absent proof of inequitable conduct, the examiner's or the applicant's absolute compliance with the internal rules of patent examination becomes irrelevant after the patent has issued.

Id. at 960. Such internal agency procedures are not judicially reviewable. See Hyatt v. Boone, 146 F.3d 1348 (Fed. Cir. 1998):

Regularity of routine administrative procedures is presumed, and departure therefrom, should such have occurred, is not grounds of collateral attack. Courts should not readily intervene in the day-to-day operations of an administrative agency, especially when the agency practice is in straightforward implementation of the statute.

Id. at 1355-56.

The presumption of validity would collapse if the PTO's administration of the restriction protocols could be turned into satellite litigation of patent-destroying consequence. In American Hoist & Derrick Co. v. Sowa & Sons, Inc., 725 F.2d 1350 (Fed. Cir. 1984) the court referred to

the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more [patent] examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents.

Id. at 1359.

## Restriction is a Discretionary Requirement

No statute defines the parameters of the examiner's discretion beyond the authorization of 35 U.S.C. §121, for the subject and scope of this discretion is unrelated to patentability. In In re Hengehold the court explained:

There are a host of various kinds of decisions an examiner makes in the examination proceeding -- mostly matters of a discretionary, procedural or nonsubstantive nature -- which have not been and are not now appealable to the board or to this court . . . . [A] requirement for restriction under §121 is now one of those discretionary matters no longer tantamount to a rejection of the claims, . . .

440 F.2d at 1339.

The entrusting of discretionary agency procedures to agency management is a classical administrative practice, requiring judicial restraint. See Vermont Yankee Nuclear Power Corp. v. Natural Res. Def. Council, Inc., 435 U.S. 519 (1978):

[T]his Court has for more than four decades emphasized that the formulation of procedures was basically to be left within the discretion of the agencies to which Congress had confided the responsibility for substantive judgments.

Id. at 524. In Citizens to Preserve Overton Park, Inc. v. Volpe, 401 U.S. 402, 410 (1971) the Court, interpreting the Administrative Procedure Act, stated that internal agency actions are not reviewable if either (1) Congress expressed an intent to prohibit judicial review, or (2) the decision is "committed to agency discretion."

Undoubtedly the procedures surrounding restriction requirements can be complex. An entire Chapter of the Manual of Patenting Examining Procedure is devoted to it.<sup>3</sup> By statute it is discretionary, for its purpose is administrative

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<sup>3</sup> A commentator experienced in the field states: "Many patent examiners and patent practitioners are confused by restriction practice and unity of invention practice in the [USPTO]." Jon W. Henry, Some Comments on "Independent and

convenience, not pitfalls in substantive validity. The fact that four examiners made somewhat inconsistent requirements for restriction does not change the controlling weight of the examiners' steady determination of the applicant's compliance with their requirements. A discretionary action having no substantive consequence and that is unreviewable is not a ground of patent invalidity, and is not subject to collateral attack.<sup>4</sup>

#### Remand is Inappropriate

The panel majority orders the district court to repeat its review of the restriction process, to search for flaws in the procedure, for my colleagues find it too complex for their appellate decipherment. A complex agency record is not sound reason to discard the required agency deference, or to ask the district court to repeat what the court has already done and ruled upon. Whatever the continuing force of the pre-Zurko "consonance" cases, on which the majority relies, in this case the patents at issue were the product of restriction requirements in which the examiners accepted the applicant's elections and the ensuing divisional applications. The courts lack authority to invalidate

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Distinct" Inventions of 35 U.S.C. '121 and Unity of Invention (pt. 1), 84 J. Pat. & Trademark Off. Soc'y 745, 748 (2002).

<sup>4</sup> The majority states by footnote that precedent requires de novo review of not only the lineage of continuing and divisional applications, but also of the correctness of the examiner's issuance of restriction requirements and the examiner's acceptance of the applicant's response to restriction requirements. That is an inapt enlargement of precedent, indeed the case on which the majority relies, Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline, PLC, 349 F.3d 1373 (Fed. Cir. 2003), states that "requirements for restriction under 35 U.S.C. 121 are discretionary with the Commissioner." Id. at 1378 quoting MPEP '803.01. The Manual of Patent Examining Procedure abjures the examiners to exercise care in making restriction requirements, id., but neither the MPEP nor any judicial decision removes the discretion of the Director, formerly termed the Commissioner, nor carves out an exception for restriction requirements into APA review of discretionary actions.

the patent on the basis of an asserted flaw in a discretionary procedure, here proposed after sixteen years. That these restriction requirements were varied and somewhat inconsistent cannot now penalize the patentee, who complied with them and whose compliance was accepted by all of the examiners involved in the examination. See Northern Telecom, Inc. v. Datapoint Corp., 908 F.2d 931, 938 (Fed. Cir. 1990) ("[A]ny doubt as to whether the examiner lapsed in his duty [under §121] does not increase the burden on the applicant.")

The sequence of restriction requirements was presented to the district court, who decided the question. It cannot be correct that when the examiner found no flaw in this non-substantive non-appealable procedure, the courts can later conduct a de novo search for some tenuous lapse, and invalidate any patent for which we disagree with the agency's discretionary decision. In Securities & Exchange Commission v. Chenery Corp., 318 U.S. 80 (1943), the Court discussed such discretionary administrative authority:

If the action rests upon an administrative determination -- an exercise of judgment in an area which Congress has entrusted to the agency -- of course it must not be set aside because the reviewing court might have made a different determination were it empowered to do so. But if the action is based upon a determination of law as to which the reviewing authority of the courts does come into play, an order may not stand if the agency has misconceived the law.

Id. at 94.

Compliance with a restriction requirement is an "exercise of judgment," id., and is entrusted to the Director. Each examiner in the case before us determined that the applicant had complied with the requirement that was imposed. The question of

restriction, its correctness and its compliance, cannot now be collaterally attacked as grounds of patent invalidity. The district court's decision should be affirmed.

## **Attachment Number 5**

**REDACTED**

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April 8, 2004

**VIA HAND DELIVERY**

The Honorable Jan Horably  
Clerk of the Court  
U.S. Court of Appeals for the Federal Circuit  
717 Madison Pl., N.W.  
Room 401  
Washington, D.C. 20439

Re: Bristol-Myers Squibb Company, et al.  
v. Pharmachemie B.V.  
Appeal No. 03-1077

Dear Mr. Horably:

Because there is a pending Motion For Rehearing *En Banc* in the above appeal, I am writing on behalf of all parties to inform the Court that the parties have an agreement in principle for resolving the litigation. The parties will submit a Stipulation dismissing the case early next week for the Court's approval.

Respectfully submitted,

*Robert L. Baechtold*  
Robert L. Baechtold

cc: David T. Pritikin, Esq.  
Francis C. Lynch, Esq.

AMM/agn

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